pharma (4)
دارس

"اللهم الدهر الرب خالق أطراف الأرض لا يكل ولا يعيا ، يعطي المعي قدرة ولعديم القوة يكثر شدة".

PHARMACOLOGY

Lec. 4

CNS
CNS — PNS
somatic (voluntary) — autonomic (involuntary)

* النهاردة هنكمل اللي ابتدناه المحاضرة اللي فاتت اللي هو الـ

Autonomic Nervous System

Pharmacological Considerations

* By using drugs that mimic or block (lytics) the action of chemical transmitters, we can modify many autonomic functions
* These functions involve variety of effector tissues including cardiac muscle, smooth muscle, exocrine glands, presynaptic nerve terminals.

يعني انا ممكن استخدم ادوية بتشابه الـchemical transmitters علشان اتحكم في الـ response اللي بيطلع ، بس ده طبعاً في الـ smooth m. والـ cardiac m. والـ glands المهم انه غير الـ skeletal m.

* Autonomic drugs are useful in many clinical conditions. Conversely, a very large no. of drugs used for other purposes (not autonomic drugs) have unwanted effects on autonomic function.

يعني في ادوية هي اصلاً مش autonomic زي مثلاً بعض ادوية الضغط ممكن يكون ليها تأثير autonomic ، مش كده وبس ، وبيوقف اى مرحلة من مراحل طلوع الـ neurotransmitter بس ازاي ؟!

ايه امثلة مراحل طلوع ال neurotransmitter ؟!

1- Synthesis of transmitter
↓
2- storage of ~
↓
3- Release of ~ (excitation لما يحصله)
↓
4- Combination of neurotransmitter with receptor
↓
5- Destruction or Removal of NT from site of action

وده لازم يحصل لأنه ميتفعش يفضل ماسك في ال site of action مدة طويلة علشان مايحصلش blockage . طب ايه اللي هيفكه؟
اللي بيعمل كده هي ال enzymes زي ال COMT او ال MAO
Monoamine oxidase — Catechol o methyl transferase
ال enzymes دي بتكسر ال NT علشان تفضي ال site of action.
حلو كده ؟!
طيب ... في ادوية ممكن تأخدها تأثر على اي مرحلة من المراحل اللي فوق دي وتوقف طلوع ال NT.

* The actions of drugs are considered primarly as tools for dissection & elucidation of physiological mechanism.
* Each step involved in neurotransmission represents a potential point of therapeutic intervention.

وده اللي قلناه ... ان كل مرحلة مهمة جدا علشان يطلع لي تأثير

طب تعالوا نشوف مع بعض الادوية اللي ممكن احدها لأهداف معينة لكنها بتأثر في نفس الوقت على ال steps of ch. transmission ...
← بتوقفها يعني ... الدكتور قال لازم نعرف الادوية دي ...
هنحفظها يعني ....

pre — post

Drugs that interfere with specific steps in Chemical Transmission:

Transmission step	Sympathatic Adrenergic Nerves	Para-sym. Cholinergic Nerves reserpine Guanethidine
1. Synthesis of transmitter	α-methyldopa	Hemicholinium (hemicolinium)
2. Storage of NT (*)	Reserpine (alkaloid) ↳ (antihypertensive drug)	None known
3. Release of trans	Guanethidine	Botulinium toxin (Botulinium Toxin)
4. Combination of trans to receptor	- prazosin (α-receptors) blocker - propranolol (β-receptors) blocker (used as antihypertensive drugs)	- Atropine (muscarinic) - d-tubocurarine (nicotinic receptor) (d-tuboCurarine)
5. Destruction or removal of trans from site of action	- Tolcapone (COMT inhibitor) - phenelzine (MAO inhibitor) - Tricyclic antidepressants (inhibit neuronal transport)	- physostignine (cholinesterase inhibitor) (physostignine)

COMT → Catechol o-methyl transferase.
MAO → Monoamine Oxidase.

Tolcapone phenelzine

(*) The transmitter after being synthetized must be stored in vesicles to be used to avoid being destroyed by the enzymes. → then this NT is released due to Ca^{+2} ions

مشتاق ريسة مشوخة كل ده 0000

Adrenergic (symph.)

- α methyl dopa
- reserpine
- Guanethidine
- [prazosin
  propranolol
- [tolcapone
  - phenelzine
  - Tricyclic

Cholenergic (Para -

- hemicholinium
- —
- Botulinum toxin
- Atropine
- [d tubocurarine
- physostigmine

pre — post

Drugs that interfere with specific steps in Chemical Transmission :

Transmission step	Sympathetic Adrenergic Nerves	Para-sym. Cholinergic Nerves
1. Synthesis of transmitter	α. methyldopa	Hemicholinium (hemicolinium)
2. Storage of N.T.*	Reserpine (alkaloid) (antihypertensive drug)	None known
3. Release of trans.	Guanethidine	Botulinium toxin (Botulinium Toxin)
4. Combination of trans. to receptor	- prazosin (α receptors blocker) - propranolol (β receptors blocker) (used as antihypertensive drugs)	- Atropine (muscarinic) - d. tubocurarine (nicotinic receptor) (d-tubocurarine)
5. Destruction or removal of trans from site of action	- Tolcapone (COMT inhibitor) - phenelzine (MAO inhibitor) - Tricyclic antidepressants (inhibit neuronal transport)	- physostigmine (cholinesterase inhibitor) (physostigmine)

reserpine
Guanethidine

COMT → Catechol o- methyl transferase.
MAO → Monoamine Oxidase.

Tolcapone
phenelzine

* The transmitter after being synthetized must be stored in vesicles to be used to avoid being destroyed by the enzymes. → then this NT is released due to Ca^{+2} ions

مشمشة رسمة مشوحة كل oooo

** Cholinergic Transmission **

choline

choline

Na^+

Na^+

Ac CoA

Na^+

Ach

synaptic vesicle

Ca^{+2}

Ca^{+2} → ⊕

presynaptic receptor

choline

acetate

Ach

postsynaptic receptor

[1] Synthesis of Acetyl choline

- transport of choline
- Inhibited by hemicholinium.

[2] Uptake into storage vesicles

to protect Ach from degradation.

[3] Release of Neurotransmitter.

- Release blocked by botulinium toxin.
- Spider venom → ↑ release of Ach.

[4] Binding to Receptor

- post synaptic receptor is activated by binding of NT
  inhibited by Atropine (muscarinic)
  d-tubo Curarine (Nicotinic)

[5] Degradation of Ach

- Ach is rapidly hydrolysed by cholinesterace in the synaptic cleft.
  inhibited by physostigmine

[6] Recycling of Choline

- choline is taken up by neuron.

CAT → Synthesis
Cholinesterase → degredatn

* Some Notes on the diagram:

impulse → (Polarizatn) + Depolarizatn
Na^+

① Synthesis of Ach is catalysed by CAT enzyme (Choline acetyl transferase)

② The process of neurotransmission is voltage dependant
يعني لما الاشارة بتوصل ال Na^+ بيبتدي يدخل جوه وبالتالي بيحصل depolarization وتغيير في ال memb. potential فال Na^+ channels بتفتح وتدخل Na^+ والحتة اللي جنبها بتحس بتغيير ال potential ده فتفتح برده وتدخل Na^+ وهكذا بتستمر ويحصل propagation على ال membrane ويجين ال Ca^{+2} يبتدي يدخل وده يشجع ال vesicles علشان تطلع ال Ach اللي جواها

* Release of Ach from vesicles is done by "Exocytosis".

③ Ach is degraded by cholinesterase enzyme into:

Choline → recycled for new neurotransmission

Acetate → recycled in krebs' cycle to Acetyl CoA (Ac CoA)

④ Presynaptic receptor:

• ده اللي هو ال receptor اللي قبل ال synapse
طب وده ايه ده ؟!
• ده بيمسك فيه Ach برده زيه زي ال post synaptic receptor
طب ايه الفرق بقى ؟!
• الفرق ان لما بيمسك فيه ال Ach بيحصل regulation ويمنع طلوع Ach اكتر ← بيتحكم في العملية يعني

• Presynaptic receptor is responsible for regulation (i.e. control)
ie// Acts as a negative (-ve) feed back.

of release of more Ach (-ve feed back mechanism)

طيب ، دلوقتي هنشوف بقى الـ cholinergic agonists اللي هم الادوية اللي شبه الـ Ach . وبتمسك في الـ receptors بتاعته.

Cholinergic Agonists

↳ "Cholinomimetics". حلوة أوي الكلمة دي

2 types

Direct acting cholinomimetic agents

دي تأثيرها مباشر ، بتمسك على طول في الـ receptor

- directly binds to & activate :
  - muscarinic (peripheral)

  or
  - nicotinic (central)

  receptors

Indirect acting agents.

دي تأثيرها غير مباشر ، دي مش على الـ receptor على طول ، امال ايه ؟!

دي بتقلل الـ cholinesterase الـ هو بيكسر الـ Ach ← يبقى الـ Ach هيزيد

← يبقى التأثير زي الاول بس بطريقة غير مباشرة.

- Indirect acting agents produce their effect by ↓ acetylcholine-esterase → so ↑ endogenous Ach conc. → and the XSS Ach in turn stimulates cholinoceptors to evoke increased responses.

Symph. (Adrenergic) — Ach — Nm — AD NA — α β

Parasym. (Cholinergic) — Ach — Nm — Ach — muscarinic

بس خد بالك ، الزيادة دى مفروض ليها حد ، لانى لو فضلت
ازود ال Ach كده من غير تفكير يبقى "اللى يزيد عن حده يقلب
ضده" وممكن تقلب بشلل فى العضلة وتقلب بالعكس زى ماحصل
فى ال conc. nicotine & dil.nicotine اللى شفناهم فى الحلى ....
وتبقى كده antagonists بعد ما كانوا agonists ....

طيب نشوف حاجة تانية اللى هى :

CHOLINERGIC RECEPTORS

من اسمها كده ... هى دى ال receptors اللى بيشتغل عليها Ach.
وهى نوعين
M → Muscarinic (mAch Rs)
N → Nicotinic (n Ach Rs)

بس كل واحدة منهم سواء ال M او ال N متقسمة تانى على حسب الاماكن اللى هى موجودة فيها ...

* 3 main (mAch Rs) occur :

a) M_1 receptors "neural" : → in CNS, gastric parietal cells.
- It is selectively blocked by 'Pirenzepine'

b) M_2 receptors "cardiac" : → in heart, also mediate presynaptic inhibition

c) M_3 receptors "glandular" : → in exocrine glands, smooth muscles & causing vascular relaxation (i.e. in muscles lining blood vessels)

Pirenzepine
Pirenzepine
Pirenzepine

* All mAchRs are expressed in CNS, activated by Ach (non selective muscarinic stimulant) & inhibited by atropine (non selective muscarinic inhibitor)

* nAchRs (Nicotinic Ach Receptors) → 2 types:
  - N_N (Nicotinic neuronal) Central
  - N_M (~~Nicotinic muscular~~) Peripheral

neuronal / muscular

• Muscular, Neuronal (or peripheral, central) nAchRs differ in their molecular structure & pharmacology:

neuronal

* N_N receptors: → in autonomic ganglia, adrenal medulla, CNS.
  • Antagonized by: trimethaphan & hexamethonium
  inhibited by

* N_M Receptors: → In skeletal neuromuscular junction
  • Antagonized by: d-tubocurarine, gallamine, atracurium & Suxamethenium (succinyl choline)

persistent depression او بعدها contraction يعني initial stimulation بيعمل ده
relaxation يعني ← بيعمل paralysis (شلل) للعضلة

muscarine
Nicotine
* alkaloid

* ester of choline
Ach

طيب تعالوا نتكلم بالتفصيل اكتر شوية عن ال :

Direct Acting Cholinomimetics

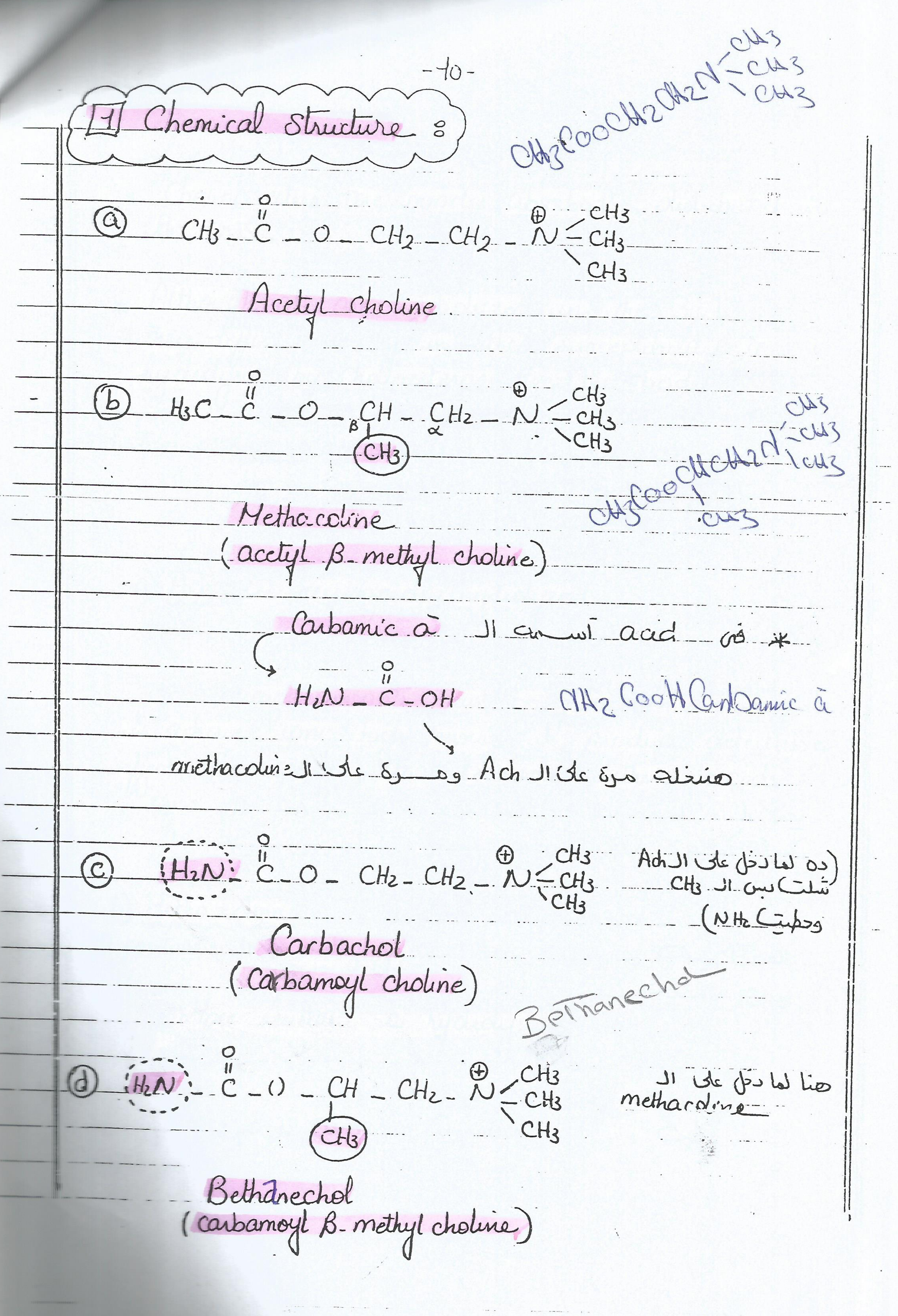
احنا قلنا ان دول اللى بيشتغلوا على ال receptor على طول فبيبقوا حاجات شبه الـ Ach او بمعنى اصح ممكن نقول esters of choline ومن ضمن ال esters دى ال Ach ...

* The direct acting cholinomimetics can be divided on basis of chemical structure into esters of choline (including Ach) or alkaloids as : muscarine, nicotine.

* A few of these drugs are highly selective for muscarinic or for nicotinic receptors but many have effect on both receptors as "acetyl choline".
  ↳ بيشتغل على الاتنين
  احنا قلنا انه (nonselective)

* هنشوف كم عنوان كده وكلام تبع ال Direct acting cholinomimetics اللى هم :
  1- Chemical structure
  2- Pharmacokinetics
  3- Pharmacodynamics
  4- Organ effects ↳
  يعنى بيعملوا ايه فى ال organs (ايه التأثير بتاعهم ؟)

يلا نشوف عنوان عنوان كده بالراحة ...



[1] Chemical structure :

$CH_3COOCH_2CH_2N(CH_3)_3$

ⓐ $CH_3-\overset{O}{\overset{\|}{C}}-O-CH_2-CH_2-\overset{\oplus}{N}(CH_3)_3$

Acetyl choline

ⓑ $H_3C-\overset{O}{\overset{\|}{C}}-O-\underset{\beta}{CH}(CH_3)-\underset{\alpha}{CH_2}-\overset{\oplus}{N}(CH_3)_3$

$CH_3COOCH(CH_3)CH_2N(CH_3)_3$

Methacoline
(acetyl β-methyl choline)

* فى acid اسمه الـ Carbamic a

$H_2N-\overset{O}{\overset{\|}{C}}-OH$

NH_2COOH Carbamic a

هندخله مرة على الـ Ach ومرة على الـ methacoline

ⓒ $H_2N-\overset{O}{\overset{\|}{C}}-O-CH_2-CH_2-\overset{\oplus}{N}(CH_3)_3$

(ده لما دخل على الـ Ach شلت بس الـ CH_3 وحطيت NH_2)

Carbachol
(Carbamoyl choline)

Bethanechol

ⓓ $H_2N-\overset{O}{\overset{\|}{C}}-O-CH(CH_3)-CH_2-\overset{\oplus}{N}(CH_3)_3$

هنا لما دخل على الـ methacoline

Bethanechol
(carbamoyl β-methyl choline)

2 Pharmacokinetics :

* Choline esters are poorly absorbed & distributed in the CNS.

* Although all are hydrolyzed in the GIT → they differ markedly in their susceptibility to hydrolysis by cholinesterase in the body.

ده اللى بيكسّر كل الـ esters دى بس حسب الـ ch. structure! بتاع كل واحد فيهم بيختلف تأثير الـ enzyme ده عليهم
يعنى مثلاً :

a) Ach : is very rapidly hydrolyzed
بيتكسر بسرعة أوى

∴ Large amounts must be given intravenously to achieve conc. high enough to produce detectable effects (non specific) that terminate within seconds.
يعنى علشان استخدم الـ Ach علشان يدينى تأثير جامد لازم اديه بكمية كبيرة لأنه مش بيستحمل وبيتكسر بسرعة جداً

b) Methacholine :
الفرق بينه وبين الـ Ach ← methyl gp فى الـ β position
وديه بتخليه ←
More resistant to hydrolysis

طب والـ Carbamic a esters اللى هم :

c) Carbachol & bethanechol:

are still more resistant to hydrolysis by cholinesterase & therefore have longer duration of action.

لانه بيقدر يقعد في الجسم اطول

N.B:

The β- methyl gp (in Methacholine, bethanechol) → reduces the potency of these drugs at nicotinic receptors
(i.e. more selective for muscarinic receptors)

احنا كده اتكلمنا عن الـ esters of choline ، في كمان الـ natural alkaloids
تعالوا نقول كلمتين عنهم كمان ....

* Chemical structures:

Muscarine

Nicotine

Pilocarpine

lobeline

لو ركزنا من ال structures هنلاقي ان كل ال choline esters كانوا
quaternary amm. cpds وده اللي خلانا قلنا انهم poorly absorbed in CNS

لكن هنا من ال alkaloids ← كلهم 3ry ماعدا ال muscarine
بس هو اللي 4ry وعلشان كده هو اقل واحد فيهم بيحصله
absorption

طب تعالوا نشوف ال Pharmacokinetics بتاعة ال alkaloids ...

* The 3ry natural cholinomimetic alkaloids (pilocarpine, nicotine, Lobeline) are well absorbed from most sites of administration.

a) Nicotine :→ a liquid, sufficiently lipid soluble to be absorbed across the skin.

b) Muscarine : 4ry amine
- less completely absorbed but is toxic when ingested & even enters the brain.

c) Lobeline : is a plant derivative similar to nicotine.

* These amines are excreted chiefly by the kidneys.
- Acidification of urine → accelerates the clearance of 3ry amines.

زي ما اخدنا، لو فاكرين، في المحاضرة التانية لما قلنا ان ال weak bases بيحصلها entrapment في ال low pH لذا لما نعمل acidification لل urine، مش هتعرف ان يحصلها reabsorption وبالتالي هيحصلها clearance و excretion.

طيب تعالوا نشوف ثالث عنوان وهو :

[3] Pharmacodynamics :

يعنى الادوية دى بتشتغل ازاى على الجسم .

* Mechanism of action:

a) **Muscarinic receptors**: G-protein Coupled R (phospho-lipase C / cAMP)

activation of muscarinic receptors implicates DAG in the opening of smooth muscle Calcium channels → IP3 releases Calcium from endoplasmic & sarcoplasmic reticulum (for M_3).

مهم كل الرايح فى المحاضرة

Activation of receptors also ↑ K^+ flux across cardiac cell membranes (M_2)

This effect is mediated by the binding of an activated G protein directly to the channel.

الكلام ده مشروح حلو فى المحاضرة الكافات ...
ارجعوا اقروه من هناك ...

b) **Nicotinic receptors**: Ion-channel Coupled R

When occupied by an agonist → causes a conformational change in the protein (i.e. channel opening) → allows Na^+ ions to diffuse down their conc gradient rapidly.

* Binding of an agonist to the receptor → ↑ the probability of channel opening & depolarization of the nerve cell or neuromuscular end plate membrane.

طب لو زاد الـ agonist ده هيحصل ايه ؟

Prolonged agonist occupying of the nicotinic receptor abolishes (يقلل اوى او يوقف) the effector response, i.e. the post ganglionic neuron stops firing & the skeletal muscles relax.

i.e. it prevents electrical recovery of the post junctional membrane, thus a state of "depolarizing blockade" is induced.

ايه الكلام الكبير ده ؟!

انا الطبيعي انى بحط الـ agonist هيمسك في الـ receptor ويدينى الـ effect اللى هو مثلاً contraction بتاع عضلة ، جميل !!
طب انا لو زودت جرعة الدواء ده ، هل التأثير هيزيد ؟!
للأسف لا ، هنا " اللى يزيد عن حده يقلب ضده " فالكمية
الدواء بيزيد اوى هيوقف العملية ويحصل relaxation of muscle
وكده يبقى الـ receptor حصله blocking زى اللى حصله الـ conc nicotine.

احنا كده أخدنا ٣ عناوين تحت الـ Direct acting cholinomimetics
فاضلنا آخر عنوان وهو الـ :
4- organ Effects
وهنشوف فيه تأثيرها على :
- eye.
- CNS
- Neuromuscular junction.

معلش ← قبل ما نبتدي ، ف حتة كده الدكتور شرحها علشان يسهل الفهم بتاع العين وازاي بتعمل accomodation for near or far vision.

① Parasympathatic stimulation :

ciliary body
ciliary muscles
iris
pupil
lens
suspending ligaments
circular muscles (constrictor muscles)

اللي بيحصل ان ال ciliary muscles بيحصلها contraction

↓

∴ ligaments will be relaxed

↓

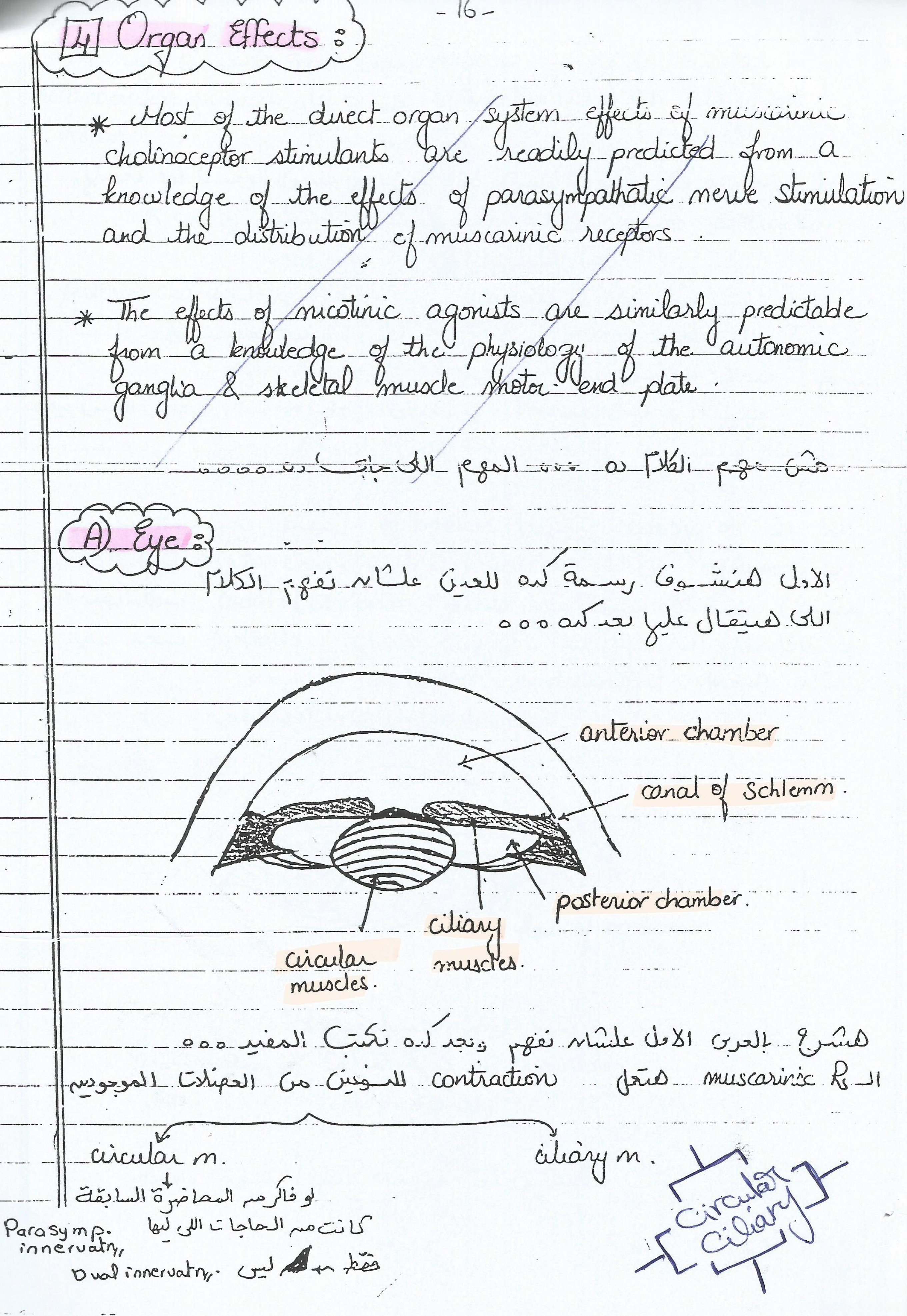
∴ lens is more convex → accomadation for near vision.

② Sympathatic stimulation :

ciliary muscle relaxed
ligaments stretched
lens flat

عكس ال parasymp.

ciliary muscle relaxed → ligaments stretched → lens is flat or less convex → accomodation for far vision.



[4] Organ Effects :

* Most of the direct organ system effects of muscarinic cholinoceptor stimulants are readily predicted from a knowledge of the effects of parasympathatic nerve stimulation and the distribution of muscarinic receptors.

* The effects of nicotinic agonists are similarly predictable from a knowledge of the physiology of the autonomic ganglia & skeletal muscle motor end plate.

هش نهتم الكلام ده ... المهم اللي جاي ده .....

A) Eye :

الاول هنشوف رسمة كده للعين علشان تفهم الكلام اللي هيتقال عليها بعد كده ...

هشرح بالعربي الاول علشان تفهم ونجد كده نكتب المفيد ...

الـ muscarinic Rs هتعمل contraction للنوعين من العضلات الموجودين

circular m. — ciliary m.

لو فاكرين المحاضرة السابقة كانت من الحاجات اللي ليها Parasymp. innervatn, فقط و ليس [illegible] Dual innervatn,

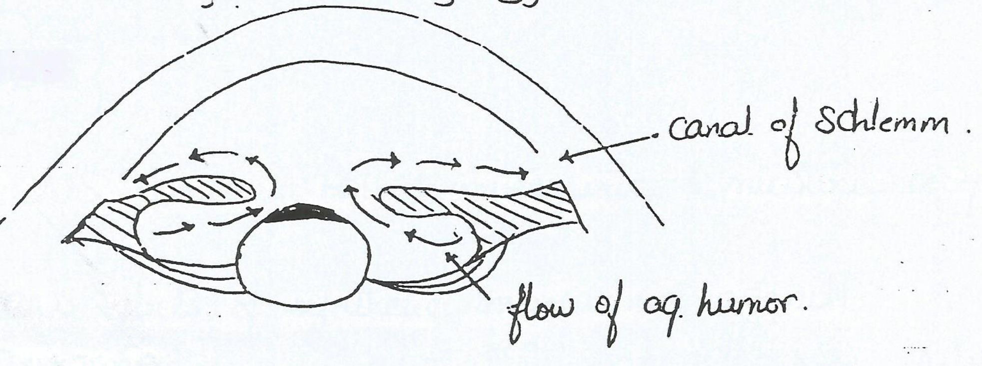
Circular
Ciliary

ال circular m. هتقل ، يعنى myosis يعنى الحدقة هتضيق ، اما ال ciliary m. لما يحصلها contraction ← هتعمل accomodation for near vision

علشان يعنى بيشوف كويس ... بس فى نفس الوقت لما يحصلها contraction هتبعد عن ال ... ، طب وايه الفكرة فى كده ؟
اقولكم انا الفكرة ...

فى حاجة اسمها aqueous humor ده بيتعمل فى ال posterior chamber وبيروح لل anterior chamber ويتخزن هناك .. ده مسئول انه يضبط ضغط العين ... حلو ؟!
طيب ، بس مينفعش يزيد اوى علشان كده ضغط العين بيزيد وده مش كويس ، فلازم اتخلص منه ، بس ازاى ؟!

لما ال ciliary m. بيحصلها contraction بتفتح فتسمح بمرور ال aq. humor من ال posterior ch. ، طب وبعدين ، هيروح فين ؟! معروف فى قناة بيروح ليها اسمها canal of schlemm. بس القناة دى قافل عليها ال ciliary m. لكن لما بيحصلها contractn بتبعد عنها وبالتالى هيحصل لل drainage لل aq. humor ده ...
زى الرسمة اللى جاية دى ...



يارب اكون عرفت اوصل المعلومة ....
وعلى العموم انا تحت امركم لو لسة مش واضحة ...

تعالوا نكتب الكلمتين دول بطريقة انظف شوية ....

* Muscarinic agonists instilled into the conjunctival sac causes contraction of :

  Circular muscle
  1. the smooth muscle of the iris sphincter → resulting in miosis (circular Muscles or, Constrictor pupile)

  2. the ciliary muscle → resulting in accommodation for near vision

* As a result → ⓐ the iris is pulled away from the angle of the anterior chamber & ⓑ the trabecular meshwork at the base of the ciliary m. is opened.

  canal ال عاى دى اللى ناتلة

↓

Both effects facilitate aqueous humor outflow into the canal of Schlemm, which drains the anterior chamber.

Antinociceptn

B) CNS :

* The CNS contains both : muscarinic & nicotinic receptors.

* The CNS effects of synthetic muscarinic agonist "Oxotremorine" are : tremor رعشة , hypothermia لدرجة الحرارة and antinociception ضد الاحساس بالالم
- These effects were Lacking in mice with homozygously mutated M_2 receptors.

Oxothremorine
- Tremor رعشة
- hypoThermia ↓ Temp
- antinociceptn ضد الإحساس بالالم

Oxotremorine

antinociceptn

* The mild alerting action (منبه) of nicotine absorbed from inhaled tobacco smoke is the best known of CNS effects.
↓
In larger conc., nicotine induces → tremors (رعشة), emesis (vomiting) and stimulation of the respiratory centre
↓
At still higher levels → nicotine causes convulsions (تشنجات) which may terminate in fatal coma.

والتأثير بتاع ال nicotine ده خلاهم بيستخدموه ك insectiside بس non selective هيقتل الحشرات وهيضر الانسان كمان.

* DiMethylPhenyl Piperazinium (DMPP) → (a synthetic nicotinic stimulant used in research) is relatively free of these central effects as it doesn't cross the bbb
وعشان كده مش بيوصل للمخ ومش بيدي ال CNS effects زي اللي فوق .....

bbb: Blood brain barrier.

وآخر حاجة هنشوف التأثير عليها هي:

c) Neuromuscular Junction:

* The nicotinic receptors on the neuromuscular end plate respond to: acetyl choline & nicotine.

Dimethyl phenyl

* When a nicotinic agonist is applied directly → an immediate depolarization of the end plate results, caused by increased permeability to Na^+ & K^+ ions. → causing contraction of the muscle.

* Depolarizing nicotinic agonists that are not rapidly hydrolyzed (like nicotine itself)

يعني مش بيتكسر بسرعة فيفضل شاغل ال receptor

↓

cause rapid development of depolarization blockade.

* طيب احنا كل ده كنا بنتكلم عن ال Direct acting cholinomimetics

وحكينا عنهم بالتفصيل الممل ..

تعالوا دلوقتي نشوف بقى الـ:

Indirect Acting Cholinomimetics

هنتكلم فيهم زي التاني عن :

1. Chemistry
2. Pharmacokinetics.
3. Pharmacodynamics (MOA)
4. Effects → CNS
   → CVS

يلا نشوف واحد واحد منهم ....

inDirect Acting Cholinomimetic

[↓ Cholinesterase] → ↑ Ach

Simple alc. ē 4ry Amm. gp
(non covalent bond)
e.g
Edrophonium → Pooly absorbed so oral conc. > Parentral

Carbamic ā ester of alc. ē 4ry-3ry Amm. gp.
(Covalent reversable)
-eg
3ry Amm. → Physostigmine → well absorped Topically → Toxic effect
4ry Amm. → Neostigmine → Pooly absorbed

(organophosphates) organic Derivatives of phosphoric ā
(Covalent irrecersable)
e.g
Echothiophate → Highly Polar Comp. more stable Than organophosphes ↓ absorptn

Triophosphat

Parathion
- not detexified in vertebrates
- non selective

lipids so rapidly absorbed

→ oxygen analogue

metathion
- rapidly metabolized into inactive products → birds mamals not insects
- Selective

1 CHEMISTRY :

احنا طبعاً عارفين ان الـ gp ده بيشتغل عن طريق ↓ cholinesterase enz.
اللي بيكسر الـ Ach و هنشوف الكلام ده بالتفصيل الآن في الـ MOA

* The commonly used cholinesterase inhibitors fall into 3 chemical groups :

(1) Simple alcohols bearing a 4ry ammonium gp (non covalent binding) eg: "Edrophonium"

(2) Carbamic a. esters of ~~alcohols bearing 4ry or 3ry~~ amm. gps (carbamates, eg: "Neostigmine" (4ry) or (3ry) "Physostigmine") → (covalent reversible)

(3) Organic derivatives of phosphoric a. (organophosphates, eg: "Echothiophate") → (covalent irreversible)

2 PHARMACOKINETICS :

* Absorption of 4ry carbamates (neostigmine, pyridostigmine) is predictably poor, ∴ much larger doses are required for oral administration than for parenteral injection.

وده طبيعي لان الـ oral route هياخد وقت اطول علشان يوصل للدم
وهو اصلاً الـ absorption بتاعه قليل فالـ هيفضل هيبقى قليل اوي
فلازم ادي جرعة اكبر من لو injection

* Physostigmine (3ry), in contrast, is well absorbed from all sites & can be used topically in the eye.
It is distributed into the CNS & is more toxic than the more polar 4ry carbamates.

لان دي ال abs. بتاعها صعب لكن ال 3ry ال absorption بتاعها
اعلى بكتير فتأثيرها بيبقى احسن وكمان يبقى toxic.

* The carbamates are relatively stable in aqueous soln..
طب هيتكسروا ازاي بعد ما يحلوا هدفهم؟!

they can be metabolized by non specific esterases in the body as well as by cholinesterase

However, the duration of their effect is determined chiefly by the stability of the inhibitor - enzyme complex, not by metabolism or excretion
يعني لما الدواء ده بيمسك في ال enzyme هيفضل ماسك اد ايه
او ال stability بتاعته عاملة ازاي ، ودي اللي هتحدد ال
duration of action بتاعته.

* The organophosphate cholinesterase inhibitors (except for Echothiophate ← مش بيتمص كويس) are well absorbed from the skin, lung, gut & conjunctiva as well as the CNS (may cause CNS toxicity)
∴ they are dangerous to humans & highly effective as insectiside. → هتقتل الاتنين.

طب ايه الفكرة من ال Echothiophate ده؟!

* (Echothiophate) is highly polar & more stable than most other organophosphates. (↓absorptn)

∴ It can be made in aqueous soln for ophthalmic use & retains its activity for weeks.

علشان مش هيحصلها absorption بسرعة

* The (thiophosphate) insecticides (Parathion, Malathion) → are quite lipid soluble & are rapidly absorbed by all routes.

• بس هل بيشتغلوا كده على طول اول ما يدخلوا الجسم؟

الاجابة: لا، طب ليه؟!

Coz they must be activated in the body by conversion to the oxygen analogue.

• طب بس احنا عارفين ان ال Malathion ده بيستخدم كمبيد حشري وفعال، طب ازاي كده وهو ممكن يضر الانسان كمان؟!

- الفكرة ان الانسان عنده mechanism تانية بتكسر ال malathion ده وتخليه inactive، ال mech. دي مش موجودة في ال insects.

* (Malathion) is also rapidly metabolized by other pathways to inactive products in birds & mammals but not in insects → ∴ it is considered safe enough for sale to the general public (i.e. selective)

But,, (Parathion) is not detoxified effectively in vertebrates (i.e. not safe)

3 MOA : (Mode of Action)

* Generally : Cholinesterase inhibitors ↑ the conc. of endogenous Ach at cholinoceptors by inhibiting acetylcholinesterase.

دى فكرة عامة كده عن اللى بيحصل ؛ تعالوا نشوف اصلاً الـ enzyme ده بيكسر الـ Ach ازاى وبعدين نشوف ازاى الادوية دى بتقلل الـ enzyme.

Serine

* MOA of cholinesterase on Ach :

Ach binds to the enzyme's active serine site

↓

then Ach is hydrolyzed, yielding (1st step)

- choline
- acetylated enzyme

↓ (2nd step)

The covalent acetyl enzyme bond is split with the addition of water (Hydration) producing

- acetate
- Free enzyme ready for binding to a new Ach molecule

طيب الادوية دي لما بتمسك في ال enz. ده تعمل ايه ؟!

* MOA of cholinesterase inhibitors on cholinesterase enz.:

لما ال Carbamates هي اللي هتمسك:

(1) The Carbomylated enzyme is considerably more resistant to the 2nd (Hydration) process → and this step is correspondingly prolonged to 6 hrs.

(2) The covalent phosphoylated bond (as in organophosphates) is extremely stable and hydrolyzes in water at a very slow rate.

* The phosphoylated enzyme complex may further undergo a process called "aging"

• ايه دي ؟!
احنا قلنا ان phosphoylated enz. complex بيبقى stable أوي وبيقعد فترة طويلة، فممكن تحصله aging اللي هي بينكسر فيه bond من ال bonds اللي بين ال oxygen وال phosphorous وبالتالي ده هيقوي اكتر ال complex اللي بين ال phosphorylated cpd & enz. ومنخليهاش تتكسر خالص حتى بعد مدة طويلة

• طيب هو انا اصلا ممكن ازاي افك ال complex ده ؟!
بيتفك ب strong Nucleophils زي دواء اسمه Pralidoxime ويرجع ال cholinesterase. بس ده مش هيحصل غير لو اديته قبل ما يحصل ال aging

* The process of Aging: involves the breaking of one of the oxygen - phosphorous bonds and further strengthens the phosphorous - enzyme bond.

Pralidoxime

- If given before aging has occured, strong nucleophiles like "Pralidoxime" are able to split the phosphorous-enzyme bond & can be used as "Cholinesterase regenerators" for poisoning

4 EFFECTS :

* The most prominent pharmacological effects of cholinesterase inhibitors are on: the Cardiovascular system, GI system, the eye & the skeletal muscle neuromuscular junction.

* Since the key action is to amplify the actions of the endogenous Ach, the effects are similar to the effects of the direct-acting cholinomimetic agonists.

يعني الاتنين مثلاً هيعملوا contraction لو اداوا لل sk.muscle
واحد هيشتغل مباشرة على الـ muscle والتاني هيزود الـ Ach
وبرده هيعمل contraction .

* هنشوف التأثير بتاعهم على حاجتين :

1. CNS
2. CVS

① CNS :

In higher conc., the lipid soluble cholinesterase inhibitors cause generalized convulsions, which may be followed by coma & respiratory arrest.

② CVS : (CardioVascular System)

Negative chronotropic, dromotropic & inotropic effects are produced

- chronotropic → ↓ rate of contraction
- dromotropic → ↓ conduction velocity across nerve fiber
- inotropic → ↓ force of cardiac contraction.

* لأن فى rest مش محتاجة اقف ! القلب ويبقى حاجه ...

• كده خلصنا الـ Indirect Acting cholinomimetics

• تعالوا نشوف دلوقتى ٤ موضوعات صغيرة والمواضيع دى عامة بين الـ direct والـ indirect :

1. Clinical uses of cholinomimetics : a) Eye
b) GI & urinary tract
c) Neuromuscular junctⁿ
d) CNS

2. Toxicity
3. Toxic manifestations
4. Managment.

معلش ... انا عارفة انى كده طولت عليكم اوى .. بس خلاص هانت ... الجزء اللى فاضل مش كبير ....

* Clinical uses of cholinomimetic :-

[1] Glucoma → open angle glucoma (chronic - simple)
→ closed " " (Acute. narrow)

[2] G.I.T & U.T.I e.g Bethanechol.
Neostigmine
Pilocarpine

G.I.T ↓ regulate ↓ motility Postoperative

U.T.I ↓ urinary Retention Postoperative & Post partum

[3] C.N.S Tt of Alzehimer

e.g Tacrine - donepezil - Rivastigmine
↓ once dialy ??
half long life time and lack of Hepatotoxic effect of Tacrine

metrifonate ↓ Tt schisto somiasis

[3] Neuromuscular junctn disease (myastTenia gravis)

e.g • Edrophonium
• Neostigmine

[1] Clinical Uses of Cholinomimetics

(A) EYE:

الأول هنحكى شوية كده عن مرض الـ Glaucoma اللى هو المية الزرقاء

* **Glaucoma:** a disease of the eye characterized by increased IOP (Intraocular pressure), atrophy of optic nerve → and produces defects in vision field.

(Glaukos = bluish green)

* طب المرض ده فى منه نوعين:

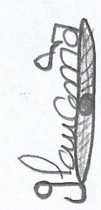
i- **Open angle glaucoma:**

1ry glaucoma in which aqueous humor has free access to the trabecular mesh work.

• Synonyms: Chronic or Simple glaucoma.

open angled

(1) الوضع الطبيعى بس هنا العملية بتحصل بصعوبة شوية بس بتفتح عادى
والـ aq.humor بيطلع بس عقبال ماده
بيحصل بيكون الضغط زاد. وبما ان القناة
مفتوحة بنسميها open angle glaucoma



النوع التاني بقى هو:

2- Angle Closure Glaucoma:

Ty glaucoma in which contact of iris with the peripheral cornea excludes aqueous humor from the trabecular drainage mesh work.

- Synonyms: Acute glaucoma, closed angle glaucoma, narrow angle glaucoma.

Closed

iris

هنا ال iris قافلة على ال cornea بطريقة مغطية على ال canal وبتمنع drainage of aq. humor وبالتالي الضغط IOP عمال يزيد جامد وممكن يسبب العمى ....

فهمتوا ايه هي المية الزرقاء دي ؟!
كل الحكاوي دي علشان نفهم الكلمتين اللي جايين دول ...

ازاي بنستخدم ال Cholinomimetics علشان اعالج ال Glaucoma ؟

* In the past, glaucoma (↑ IOP) was treated with either direct agonists (pilocarpine, methacholine, carbachol) or cholinesterase inhibitors (physostigmine, demecarium, echothiophate, isoflurophate (Diisoflurophate) DFP as ointment)

* For chronic glaucoma, these drugs have been replaced largely by topical β- Blockers & Prostaglandin derivatives.

* يعني ايه ؟!
احنا عارفين ان سبب ال glaucoma هو ضغط عالي
في العين وسبب الضغط ده اني بيطلع خنك aq. humor ومش
بعرف اتخلص منه . طب ما انا ممكن احل الموضوع دي باني اقلل
اصلاً طلوع الـ aq. humor وهو ده اللي بيعمله ال β- Blockers
تبقل طلوع الـ aq. humor ← treatment ..

(B) Gastrointestinal & Urinary Tracts:

i.e: using of cholinomimetics in → G.I.T & U.T.I ???

(1) In clinical disorders that involve depression of smooth muscle activity without obstruction

(2) Postoperative ileus (atony or paralysis of stomach or bowel following surgical manipulations)
بعد العمليات الجراحية بيبقى فيه لخبطة في حركة ال GIT فلما ادي
الادوية دي هتضبط الدنيا وتعمل activation لل GIT

(3) Urinary Retention (Postoperative or Postpartum)
بعد العمليات — بعد الولادة

* The most widely used agents are:
bethanechol, neostigmine.

Bethanechol
neostigmine

* Pilocarpine has long been used to ↑ salivary secretion.

(C) Neuromuscular Junction

* "Myasthenia gravis" → a disease affecting skeletal muscle neuromuscular functions.

. Frequent findings are : ptosis (ارتخاء في جفن العين) , difficulty in swallowing & speaking , extremity weakness & ultimately respiration (Sensitivity to aminoglycoside antibiotic) (irregular)

يعني واضح انه مريض بيعمل relaxation للعضلات فالحاجة اللي

اديله حاجة تزود الـ contraction زي:

ex

1- Edrophonium : used as a diagnostic test for the disease and the long term therapy.

2- Neostigmine , pyridostigmine or ambenonium (every 4-6 hrs)

* Antidote for neuromuscular blockade following surgical anaethesia → Neostigmine & Edrophonium (IV, IM).

* Antimuscarinic drug Intoxication (by atropine, TCA)
TCA ↓ tricyclic antidepressants

دول بيعملوا blocking للـ MRs ، فعشان اعالج ده اديله

→ Physostigmine → ↑ Ach → removes competitive blocker

للـ receptor عشان تقدر تشتغل تاني

this Physostigmine can reach the CNS.

myasthenia

[Toxicity]

1) - ↑ Dose of relaxants ⟶ Paralysis
2) - ↑ Dose of Contractants ⟶ Convulsions
3) - Toxic effect of pesticides
(1° organophosphates - 2° carbamates)
4) - war nerve gases

Cholinesterase inhibitor gases have lethal effect

D CNS :

* Tacrine, donepezil & Rivastigmine are acetylcholine-esterase inhibitors that appear to have modest clinical benefit in treatment of cognitive dysfunction in Alzheimer's patients.

* Donepezil → may be given once daily, why?!
  - because of its long half life & it lacks the hepatotoxic effect of Tacrine.

* Metrifonate was used for the treatment of Schistosomiasis.

* كده خلصنا اول موضوع ooo صغير أوي ، صح ؟!
تعالوا نشوف تاني موضوع ، ودة كبير صحيح oooo

2 Toxicity

* The acute toxic effects of the cholinesterase inhibitors, like those of the direct acting agents, are direct extensions of their pharmacologic actions

يعني اللي اصلاً بيعمل relaxation يبقى لما يزيد هيعمل paralysis

واللي بيعمل contraction ← لما يزيد هيعمل convulsions

Toxic manifestations

muscarinic

DUMBELS

Diarrhea
urinatn
miosis
Bradycardia
Emesis
lacrymatn
sweat
salivatn

Nicotinic

MATCH

muscle Twitching
Adrenal hyperActivity
Tachycardia
cramping
Hipertension

C.N.S

- Confusion
- loss of coordinatn
- " " reflexes
- convulsions
- Paralysis in c Respiratory

* The major source of such intoxications is pesticide use

لما بياخدها الانسان او بيشمها بتعمله toxicity. وبالذات
اهم كتير ← 100 organophosphates & 20 carbamates

* The "war nerve gases": حرب الغازات (tabun, Sarin & Soman) are among the most potent synthetic toxins known (they are cholinesterase inhibitors) → they are lethal to Laboratory animals in nanogram doses.

3 Toxic Manifestations

يعني ايه ال symptoms بتاعت ال toxicity ؟
هنشوف ايه على الانسان ده !؟
هنشوف لو ال toxicity حصلت بسبب حاجات بتشتغل على ال Muscarinic Rs او ال Nicotinic Rs او اشتغلت على ال CNS اللي واصلها الاتنين ...

A Muscarinic:

→ miosis, salivation, sweating, bronchoconstriction, vomiting (emesis), diarrhae, bradycardia, hypotension, urination & lacrimation

نجمع اهمهم في كلمة كده قالها الدكتور علشان نعرف نفتكرهم ←

DUMBELS

- Diarrhae
- urination
- Miosis
- Bradycardia
- emesis
- Lacrimation
- sweating, salivation

DUMBEls

DUMBEls

(B) Nicotinic :

(حركات لا ارادية فى العضلات)

(contractions) ← → skeletal muscle twitchings & cramping, fasciculations & eventually severe weakness and paralysis (respiratory) due to sustained depolarization.

also adrenal hyperactivity, tachycardia & hypertension

MATCH ← تجمعهم كلمة

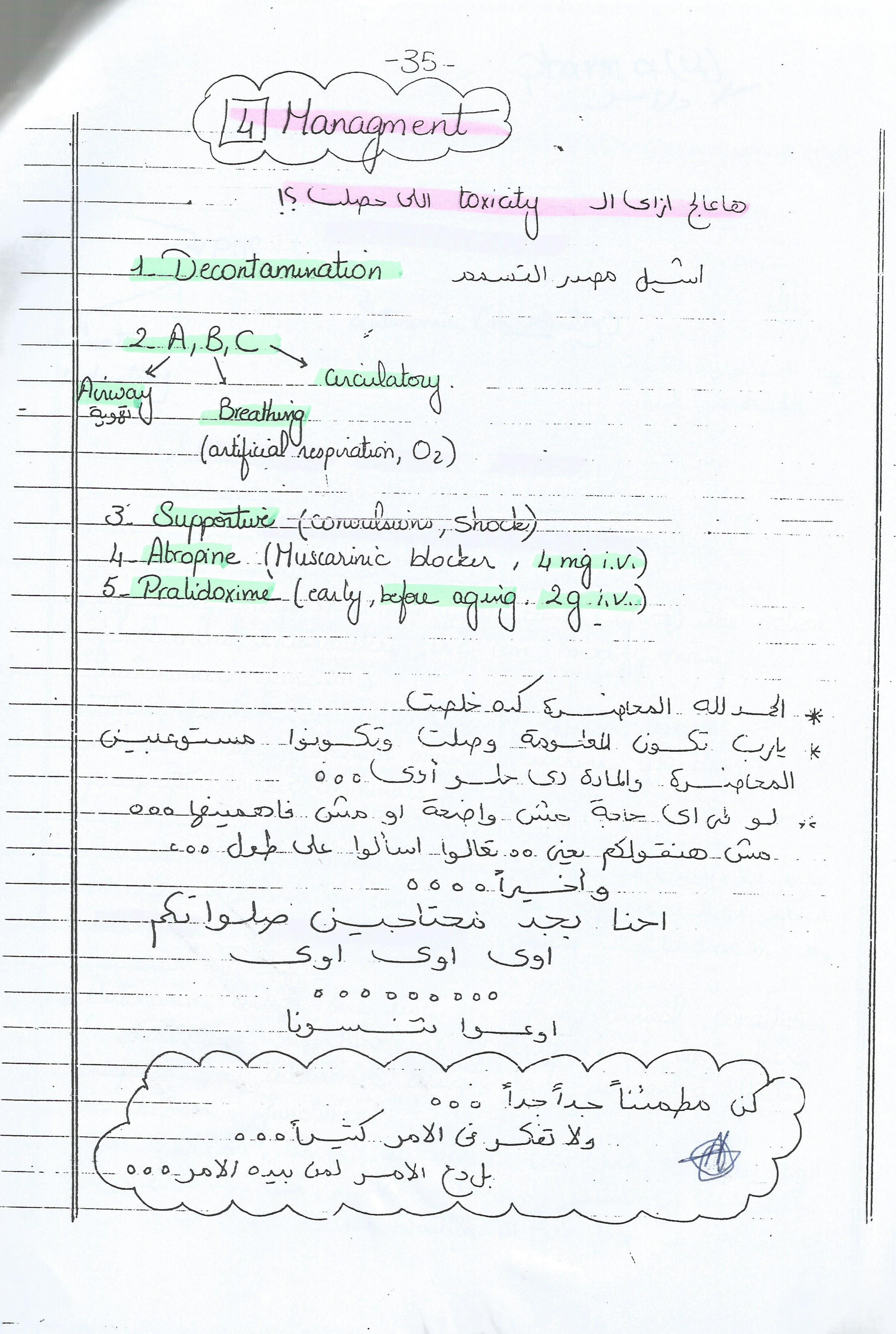
- skeletal Muscle twitchings
- adrenal hyperactivity
- tachycardia
- cramping
- Hypertension

(C) CNS :

→ confusion, ataxia (loss of coordination), loss of reflexes, convulsions, coma & central respiratory paralysis

→ Actions on the Cardiovascular centers in the medulla oblongata lead to hypotension.

وصح آخر عنوان فى المحاضرة العظيمة دى ...
معلش انا عارفة انى طولت عليكم ...
بس انا مجبتش حاجة من عندى ...



4 Managment

هاعالج ازاى ال toxicity اللى حصلت؟!

1- Decontamination اشيل مصدر التسمم

2- A, B, C
- Airway تهوية
- Breathing (artificial respiration, O_2)
- circulatory

3- Supportive (convulsions, shock)
4- Atropine (Muscarinic blocker, 4 mg i.v.)
5- Pralidoxime (early, before aging. 2g i.v.)

* الحمد لله المحاضرة كده خلصت
* يارب تكون المعلومة وصلت وتكونوا مستوعبين المحاضرة والمادة دى حلو أوى ...
* لو فى اى حاجة مش واضحة او مش فاهمينها ... مش هنقولكم بعين .. تعالوا اسألوا على طول ...

وأخيراً ....

احنا بجد محتاجين صلواتكم

اوى اوى اوى

....

اوعوا تنسونا

كن مطمئناً جداً جداً ...
ولا تفكر فى الامر كثيراً ...
بل دع الامر لمن بيده الامر ...